Review of Neurochemistry

What are neurotransmitters? ____________________________________________

In molecular terms, neurotransmitters are molecules that ___________ and ___________ of neurons by, for example, increasing or decreasing enzymatic activity or altering membrane properties.

Classes of molecules that serve as neurotransmitters:

I. Small molecules:
   A. Acetylcholine (very important at ___________ in peripheral nervous system and other synapses in the brain - CNS).
   B. Monoamines:
      a) Catecholamines
         1. Dopamine (Substantia Nigra in midbrain);
         2. Norepinephrine (noradrenaline) and Epinephrine (adrenaline)
            - ___________, respectively;
      b) Indoleamines
         1. Serotonin
         2. Histamine (found mostly in mammillary nuclei of hypothalamus)
   C. Amino acids:
      a) Excitatory amino acids (ex., glutamate, aspartate, taurine)
         - glutamate most utilized excitatory NT; ex. cortical pyramidal cells.
      b) Gamma-aminobutyric acid (GABA)
         - most widespread inhibitory neurotransmitter throughout the brain.
      c) Glycine
         - inhibitory neurotransmitter, especially in ___________, 1
         - normally inhibits motor neuron activity.
   C. Purines
      1. ATP

II. Large Neurotransmitters

Neuropeptides
   - there are at least 50 neuropeptides that act as neurotransmitters or neuromodulators (little direct activity by themselves, but modulate action of other neurotransmitters).
   - neuropeptides are normally short amino acid chains.
   - some examples of neuropeptides:
      - Endorphins (endogenous opioid analgesics of the body).
      - Substance P (involved in pain neurotransmission).
      - Corticotropin-releasing hormone (CRH - stress & anxiety).
      - Neuropeptide Y (NPY - control of feeding).
      - Vasopressin (diuretic hormone - control of drinking).

III. Soluble Gases
   1. Nitric oxide
   2. Carbon monoxide

What’s Dale’s Principle? ____________________________________________

Is this true? _____

What’s Dale’s Modified Principle? ____________________________________

______________________________________________________________

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SYNTHESIS, PACKAGING, AND TRANSPORT OF NEUROTRANSMITTERS

1. Production controlled by ____ (cell types)
2. Small neurotransmitter molecules; synthesized in ____________ (ex., acetylcholine, glutamate, GABA)
3. Large neurotransmitter molecules (peptides); synthesized in ______ (ex., endorphins, Substance P)

4. 7 CRITERIA FOR SMALL NEUROTRANSMITTER STATUS

1. ______________________________
2. ______________________________________
3. ______________________________________________________
4. ______________________________________
5. ________________________
6. ____________________________________
7. _________________________________________________

NB. Most neurotransmitters are most accurately called "putative" (supposedly) neurotransmitters because all the above criteria are difficult to obtain.

Neuropeptide status requires a different set of criteria:

1. Includes the development of ______________ to detect the putative neuropeptide (includes extraction and separation of endogenous peptide).
2. Determination of ______.
3. ____________ of peptide to test for bioactivity.
4. Production of ______ to endogenous peptide to visualize and localize neuropeptide in the central nervous system.
RELEASE OF NEUROTRANSMITTERS

1. Arrival of ______________________
2. Opening of ______________________ channels
3. Ca++ enters into presynaptic button (enters close to vesicles)
4. Ca++
5. Induces the ______________________ of synaptic vesicles to the presynaptic membrane
6. Exocytosis: neurotransmitter released into the ______________

What is quantal release? ______________________

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Action potential arrives

synaptic vesicle

Vesicle docks to membrane

Ca++ enters cell

Vesicle fuses NT released

Neurotransmitter vesicle exocytosis

Demonstration of neurotransmitter quantal release
DEACTIVATION OF NEUROTRANSMITTERS

1. _____________________________________________
   (ex., amino acids and monoamines)

2. __________________________
   (ex., acetylcholinesterase for ACh, several specific and non-specific proteinases for breakdown of neuropeptides - endopeptidases)

3. Recycling (once back inside the presynaptic membrane)

There exist 2 general types of neuronal transmission in the brain:

1. **“Wiring transmission”**: glutamate and GABA mediate ____________
   precise excitatory and inhibitory effects of one neuron on relatively few follower (other) neurons.
   - spatially precise: ______________________________________
   - temporally precise: ______________________________________

Wiring transmission is very important for? ______________________________________________________

Thus, wire transmission is nearly entirely mediated by ion channel receptors, which can quickly depolarize or hyperpolarize neurons.

2. **“Volume transmission”**: monoamines (DA, NE, EPI, 5-HT) and neuropeptides mediate ____________
   excitatory and inhibitory effects of one neuron on a large number of follower neurons (ex. human substantia nigra of humans contains roughly 10,000 neurons per side, but 1 DA neuron contacts 1000s of neurons)
   - spatially imprecise: ______________________________________
   - temporally imprecise: _____________________________________

Thus, monoamines are believed to play a role more in regulating the general excitatory and inhibitory “tone” of their targets rather than mediating specific transfer of sensory information or motor commands.

Volume transmission important for: _____________________________________________________________
RECEPTORS AND RECEPTOR SUBTYPES

The only way that a neurotransmitter can produce an effect on a target neuron is by ________.
- every receptor protein has at least 2 important functional domains:
  A. _________________
  B. _________________

1. Receptors are proteins that contain binding sites for ________.

2. “Lock and Key” arrangement

3. Receptor subtypes: Several receptor proteins can bind _________. (ex., acetylcholine binds both “nicotinic” and “muscarinic” receptors).

4. Effect of a neurotransmitter is determined by the _________.

TYPES OF RECEPTORS

There are two general types of receptors based on their type of effector domain:

1. ___________________

2. ____________________
- produces second-messenger molecules which: - _________________
  - _________________
  - _________________

- outside
- inside
PSYCHOPHARMACOLOGY

The study of the effects of drugs on the nervous system and behavior

*Drug (pharmacology):* ________________________________

Exogenous: "produced from ________" (ex., aspirin)

Endogenous: "produced from ________" (ex., acetylcholine)

What are Drug effects? ________________________________

Drug = _______

In neuropharmacology, ligands can have two general effects on synaptic transmission; they can _______ or _______ neurotransmission.

- Drugs that facilitate the effects of a particular neurotransmitter are called __________.
- Drugs that inhibit the effects of a particular neurotransmitter are called ________________.

**General principles of drug action**

**Pharmacodynamics**

- for example, a drug may block or stimulate receptors, or enzymes

**Pharmacokinetics**

- for example, drug solubility, rate of absorption, rate of metabolism.

Although pharmacodynamic factors determine the specific biological effects of a drug, pharmacokinetic factors can be very important in determining how effective a drug is (ex. why not use dopamine to treat Parkinson's disease?).

1. **Important pharmacokinetic considerations**

A. How do drugs reach their site of action?

- crossing a variety of biological barriers, for example:

1. **The epithelial cell lining of the digestive tract** -
   - epithelial surface area is ________________ than in the stomach, making it an area of choice for absorption.
   
   b. Food _______ gastric emptying (stays in stomach longer), so it is often recommended that drugs be taken on _______ stomachs to allow drug to reach the small intestines more quickly.
   
   c. A similar principle works for alcohol. It is absorbed much more efficiently in the small intestines than in the stomach so alcohol’s effects are ________________ when ingested on empty stomachs.
2) The endothelial cell lining of blood vessels -
   a. outside the brain, ______________________ allow most small molecules to pass through (fat soluble or not). Only large proteins, or protein-bound molecules are excluded.
   b. in the brain, ___________ of the endothelial cells, and astrocytes do not allow even small particles to ______________ into the brain (______________). Only fat soluble molecules diffuse into brain.

3) Neuronal membranes -
   a. steroids are examples of drugs that act inside cells and must be able to cross the cell membrane. They are able to do so because they are ____________.

B. How do drugs cross biological barriers (issue of permeability)?

1) ______________ – many small and fat-soluble molecules can directly cross (diffuse) all cell membranes without assistance. - ex. water, some gases [O, CO, CO₂, NO] and some small "uncharged" molecules [such as alcohol and steroids].
   - the net direction of movement = concentration gradient (high to low)

2) ______________ – many molecules cross membranes via channels or transporters. These are proteins embedded in cell membranes that selectively allow molecules through
   - ex. ion channels, neurotransmitter transporters.
   - net direction of movement from high to low concentration.

3) ______________ – molecules pumped against concentration gradient (from low to high concentration). These special proteins require energy (usually ATP) to carry out their task.
   - ex.: the Na⁺-K⁺-pump (ATPase)

C. How are drugs inactivated and removed from the body (clearance)?
   Biotransformation/metabolism – many substances are changed chemically (__________) while in the body and in most cases these changes ______ the substance’s biological activity and increases its ease of ______ in the urine.
   - liver enzymes play a large role in drug metabolism
   - blood circulation from digestive tract goes directly to __________
   - in order for drugs taken orally to be effective, they need to __________

So, route of administration of a drug is a very important variable.

Different routes of administration

<table>
<thead>
<tr>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous (0.6mg/kg)</td>
</tr>
<tr>
<td>Smoked (100mg base)</td>
</tr>
<tr>
<td>Oral (2mg/kg)</td>
</tr>
<tr>
<td>Intranasal (2mg/kg)</td>
</tr>
</tbody>
</table>

Some additional routes:

- IM
- SC
- PO
- Topical
- Inhalation

![Graph showing plasma concentration over time for different routes of administration]
There exist significant individual differences in pharmacokinetics that lead to substantial differences in sensitivity to pharmacological agents.

Examples of important individual factors:

- **Body weight and size** – smaller and lighter people tend to be more _____ to a particular dose of a drug (simply a _____ effect).
- **Age** – children and old people are usually more sensitive to a particular dose of a drug beyond body size
  - infants may have _____ levels of certain enzymes involved in the metabolism of drugs.
  - older individuals may also have ___________ and their biological barriers may not be as efficient in ________ drugs from absorption and entry into tissues.
- **Gender** – besides the size component, women have a greater proportion of adipose tissues and a lower proportion of water than men.
  - some fat-soluble drugs are taken up __________________ in women than men.
- **Genetic** – there are genetic differences in the __________
  - ex. individuals (especially of Asian descent) have a deficient form of the enzyme acetaldehyde dehydrogenase. This enzyme is important in the metabolism of alcohol, thus, people with a deficiency in this enzyme are much more sensitive to the "toxic" effects of alcohol, such as "flushing" of the face, sweating and nausea.

II. Important pharmacodynamic considerations:

**Mechanism of action** – invariably, drug actions are produced by interactions with a __________ present in cells.
- for CNS drugs, the functional molecule that the drug interacts with is in many cases a protein (ex. receptor, ion channel, or enzyme).
- drugs often produce more than one physiological effect. However, not all effects will display the same sensitivity (in other words the drug will be more ______ at producing one vs. another effect).

**Drug Potency vs. Efficacy**

- **Potency**: __________________
  - related to “affinity” of drug for site of action

- **Efficacy**: __________________

![Diagram of Drug Potency vs. Efficacy](image.png)
A useful drug will be very potent for producing a desired effect and not very potent for producing an unwanted ____________.

**Side-effects** (can be beneficial, but often detrimental)
- ex., barbiturates are effective in reducing anxiety, but they also reduce respiratory rate, which can lead to death (very small therapeutic index).
- death is obviously the ultimate unwanted side-effect. Many drugs when given in a high enough concentration are ________.
- the lethality of a drug is often described as the ______ – the lethal dose in 50% of individuals. This can only be determined empirically (by experiment/observation). A “good” drug produces its desired effect at much lower concentrations than the LD50.
- the effective dose of a drug is often described as the ______ – the effective dose in 50% of individuals.
- the therapeutic ratio for a drug is = ______
- a very high therapeutic ratio is desired!!!

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**Dose-response properties**

- **ED$_{50}$**: Dose of drug at which 50% of maximal effect is achieved
- **LD$_{50}$**: Dose of drug at which 50% lethality is observed
- **Therapeutic Index**: Ratio of LD$_{50}$/ED$_{50}$ (larger is better)